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Erythema Chronicum Migrans

A Possibly Infectious Disease Imported from Northern Europe

LUKE WAGNER, MD
GEORGE SUSENS, MD
LARRY HEISS, MD
RICHARD GANZ, MD
JAMES McGINLEY, MD
San Francisco

WORLD TRAVEL has extended the array of diseases with which physicians are confronted. Erythema chronicum migrans (ECM)—rarely seen in the Americas although not uncommon in the Old World, primarily Northern Europe—occurred in the patient reported here three weeks after his return from an endemic area.

ECM is a large, smooth-surfaced, annular lesion with indistinct borders; the center clears while the periphery slowly expands to enormous dimensions. It is usually single, although multiple lesions have been described.[1] ECM occurs most often in exposed skin, frequently appearing weeks or months after a tick bite.[2-4] Reported associated neurologic manifestations have included headache, hallucinations, disorientation, optic atrophy, hyperesthesia, paresthesia, radicular pain (usually in an extremity involved in the lesion), vertigo, vomiting, nuchal rigidity, and in one case paresis and anesthesia of an arm having a lesion;[5] in another case, paresis of a leg following a lesion on the thigh occurred.[1] Our patient had associated cerebrospinal fluid findings consistent with lymphocytic meningitis, and presented with bilateral facial paralysis.

Report of a Case

A 46-year-old white American man had undergone right orchiectomy and radiation therapy for seminoma in July 1968, and had been under treatment for hypothyroidism for 15 years. He left the United States on June 19, 1974, and traveled through France, Belgium, Denmark and Germany, frequently taking country walks and attending several picnics in the countryside. On July 1, he was seen in an emergency room in Germany because of headache accompanied by pain in the cervicothoracic spine, was advised to return to this country, and arrived on July 10. On July 14, paresthesia developed in the right side of the tongue, followed on July 15 by the onset of right facial palsy without sensory deficit, associated with a hot, mildly tender sensation around the neck. In the emergency room of another hospital, x-ray examination and lumbar puncture were carried out. On July 20, he noted sudden weakness of the left side of the face, and was admitted to Kaiser Foundation Hospital, San Francisco. He had taken no medicine other than propoxyphene hydrochloride, 65 mg occasionally for pain, and 0.4 mg of levothyroxine daily.

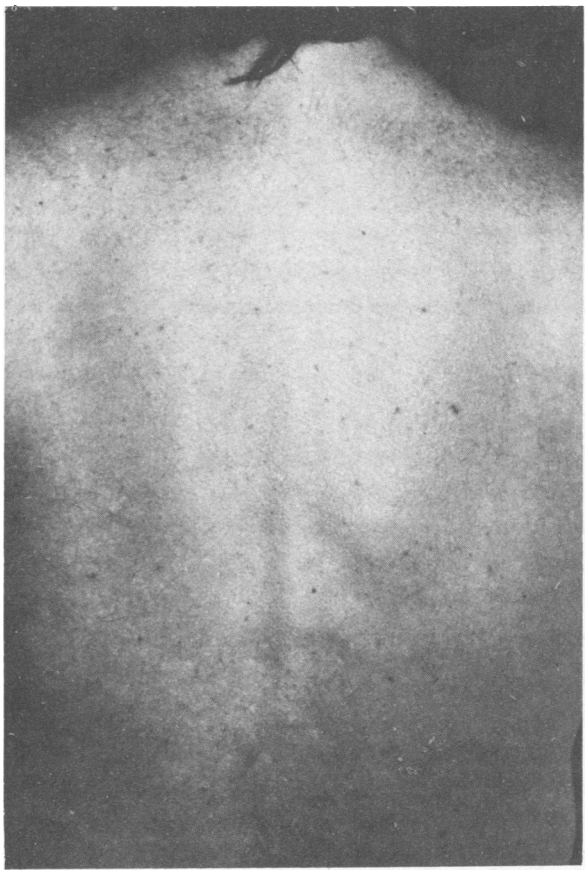

Figure 1.—The large annular lesion of erythema chronicum migrans in the patient presented.

From the Department of Medicine (Drs. Wagner, Susens, Heiss, and Ganz), and the Department of Dermatology (Dr. McGinley), Kaiser-Permanente Medical Center, San Francisco.

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Reprint requests to: George Susens, MD, Department of Medicine, Kaiser-Permanente Medical Center, 2200 O'Farrell Street, San Francisco, CA 94115.

The only abnormalities observed were a smooth, nonscaly, erythematous skin lesion 22 cm in diameter, with central clearing and indistinct edges, extending over the posterior aspect of the chest in the midline (Figure 1), its horizontal axis over the fourth thoracic vertebra. There was no tenderness along the vertebrae. Abnormal neurologic findings were weak, though present, corneal reflexes; facial diplegia, and bilateral loss of taste on the anterior two thirds of the tongue.

Hematocrit reading was 48 percent; leukocyte count, 5,800 per cu mm with a normal differential. The erythrocyte sedimentation rate (Westergren) was 24 mm per hour. Serum chemical analyses, serum protein electrophoresis, blood sugar, triiodothyronine uptake and radioimmunoassay of thyroxine showed no abnormality. Studies for rickettsiae at the Viral and Rickettsial Disease Laboratory of the State of California Department of Health showed no complement fixation titer for the spotted fever group or Q fever at dilutions less than 1:8. Response to testing for the typhus group was positive at 1:8—a finding of uncertain significance which may represent a nonspecific rickettsial antibody titer. Further studies of this specimen at the Center for Disease Control, Atlanta, Georgia, confirmed this finding but identification of a specific agent was not possible. During the acute phase, the blood showed titers of varicella and mumps viruses at 1:8; of herpes simplex at 1:64; of St. Louis encephalitis virus at 1:16. The convalescent serum showed no change in these titers, and no titer for Venezuelan or Western equine encephalitis virus. The St. Louis encephalitis viral titers may have significance in that they may reflect either earlier infection by that agent, a nonspecific elevation due to previous immunizations or cross-reacting antibodies to other Group B arboviruses, such as the tickborne group, endemic in Europe. These sera were sent to the Center for Disease Control, Ft. Collins, Colorado, where more specific arbovirus antigens are available. Hemagglutination-inhibition and complement fixation antibodies to various Group B arboviruses (Denge-2, West Nile, yellow fever, Kyasanur forest disease, Russian spring summer encephalitis, Langat, Zika, looping ill, Central European encephalitis) were elevated, and no change in titers of convalescent sera were found. The more specific neutralization tests were abandoned for technical reasons. Response to the Venereal Disease Research Laboratories (VDRL) test was negative. There was no evidence of antinuclear antibody, and C3 and C4 complement levels were normal. Findings on urinalysis were normal; appropriate studies showed no chorionic gonadotropin.

The cerebrospinal fluid was first studied July 15, at another hospital. It contained, per cu mm, 123 mg of protein (prealbumin, 1 percent; albumin, 66 percent; α_1-globulin, 5.9 percent; α_2-globulin, 8 percent; β-globulin, 9.1 percent; γ-globulin, 9.8 percent), and 56 leukocytes, all lymphocytes. On July 24, the cerebrospinal fluid contained 55 mg of protein per cu mm with an essentially normal electrophoretic pattern save for a slight increase in the percentage of albumin; 55 mg of glucose, 30 leukocytes, 99 percent lymphocytes, and showed no organisms on preparations with India ink, Gram's stain or acid-fast stain. No organisms grew on cultures, either routine or for fungus or acid-fast organisms. Response of the cerebrospinal fluid to VDRL test was negative; cytologic study showed no neoplastic cells.

No pertinent abnormalities were shown by x-ray studies of the chest or of the cervical and thoracic vertebrae; by electroencephalogram or brain scan. Findings on biopsy of the skin from the erythematous area showed one acantholytic epidermal vesicle and minor perivascular lymphocytic infiltration in the dermis, consistent with ECM. No spirochetoid bodies were noted in the skin biopsy specimen. No organisms grew on culture of the skin for aerobic and anaerobic bacteria and fungi.

During the patient's first five days in the hospital, the peripheral margins of the skin lesion expanded notably while its center cleared. On the fifth hospital day, the oral administration of 400,000 units of penicillin VK four times daily was begun. On the ninth hospital day the erythema was clearing, the facial diplegia was unchanged and the patient was discharged. One week later, the rash had cleared but the facial diplegia was unchanged. Findings on an electromyogram were consistent with bilateral nuclear or infranuclear seventh cranial nerve palsy. The patient subsequently has recovered 90 percent function of both facial nerves.

Comment

The cause of ECM has not been elucidated. Because there is evidence that it responds to antibiotics,[4,6-8] an infectious origin has been sought. Spirochetoid bodies have reportedly been found

in the skin at biopsy,[9] and positive responses to serologic tests for species of rickettsiae have been seen.[7,10] Viral causation was suggested because ECM has been associated with a meningoencephalitis similar to other tick-bite meningoencephalitides of viral origin.[2] In 1930, Hellerström[11] reported a case of ECM associated with lymphocytic meningitis, an association subsequently noted by others.[3,8,12-15] Toxic or allergic causes have been considered.[13]

The reason for central nervous system involvement is also in question. Response of these manifestations to antibiotic therapy has been reported,[3,6] but resolution of the cerebrospinal fluid abnormalities was less convincing. Thus, the concurrence of ECM and meningoencephalitis may be coincidental rather than evidence of a common cause. This was the conclusion of Putkonen and co-workers,[2] who on clinical and epidemiologic grounds inferred that the rash and the encephalitis occur coincidentally because both are transmitted by a tick, and tick-borne meningoencephalitis is endemic in Europe. In our patient there was a high stable titer to Group B arbovirus, but we were unable to discern a temporal relation between this finding and the clinical problem, or to find a specific agent responsible for the elevated titer.

The diagnosis of ECM is primarily clinical, depending on a history of exposure, the appearance of the lesion and possibly its response to antibiotics. Appearances on skin biopsy are nonspecific, and the finding of spirochetoid bodies inconsistent,[9] as are those on serologic studies for rickettsiae.[7,10] Some workers have injected extracts of the tick Ixodes reduvius into the skin and observed that the characteristic lesion was induced in patients with ECM but not in normal volunteers[3]—a test that is neither practical nor standardized. Like 50 percent or more of patients with the disease,[3,4] our patient had no history of tick bite; but he had been amply exposed, and the period that had elapsed between exposure and the initial manifestations of disease were appropriate to incubation time. Further, the lesion appeared to respond to penicillin, although spontaneous regression cannot be ruled out.

Drug sensitivity, internal neoplastic activity and fungal infection were considered as possible causes. The patient had used propoxyphene minimally, and had taken it from time to time over months before the lesion developed. We found no report of the association of ECM with propoxyphene ingestion. Neoplasia was unlikely in this otherwise healthy man who had survived removal of the seminoma longer than five years without evidence of recurrence; attempts to find metastatic tumor proved futile. The clinical course and negative cultures made a fungal origin unlikely.

The patient also had lymphocytic meningitis, perhaps unrelated to the skin lesion. A lymphocytic reaction in the cerebrospinal fluid has been known to be associated with bilateral facial paralysis; however, the temporal coincidence of the cutaneous and neurologic aspects of our patient's illness suggest that they were related. Focal neurologic abnormalities in ECM have been noted previously only in extremities that were the site of the cutaneous lesion.[1,5] We are not aware of reports of cranial nerve involvement.

Summary

Erythema chronicum migrans, seen rarely in the New World, occurred in an American who had visited rural Northern Europe. Although many cases have followed tick bite, the cause of the disease is unknown. It has frequently been accompanied by neurologic manifestations. The patient reported here presented with bilateral facial paralysis and cerebrospinal fluid evidence of lymphocytic meningitis.

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